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Phenotypic spectrum associated with SPECC1L pathogenic variants

new families and critical review of the nosology of Teebi, Opitz GBBB, and Baraitser-Winter syndromes

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Comparison of survival after aortic valve replacement with Mitroflow or Perimount prostheses

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Comparison of survival after aortic valve replacement with Mitroflow or Perimount prostheses

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1.1 Conflict of interest statement

Dr. Aasbjerg has nothing to disclose.

Dr. Mortensen reports personal fees from Edwards Life Science (TAVI proctor), outside the submitted work;.

Dr. Nørgaard has nothing to disclose.

H. C. Rytgaard has nothing to disclose.

T. A. Gerds has nothing to disclose.

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Dr. Kober has nothing to disclose.

Dr. Nielsen has nothing to disclose.

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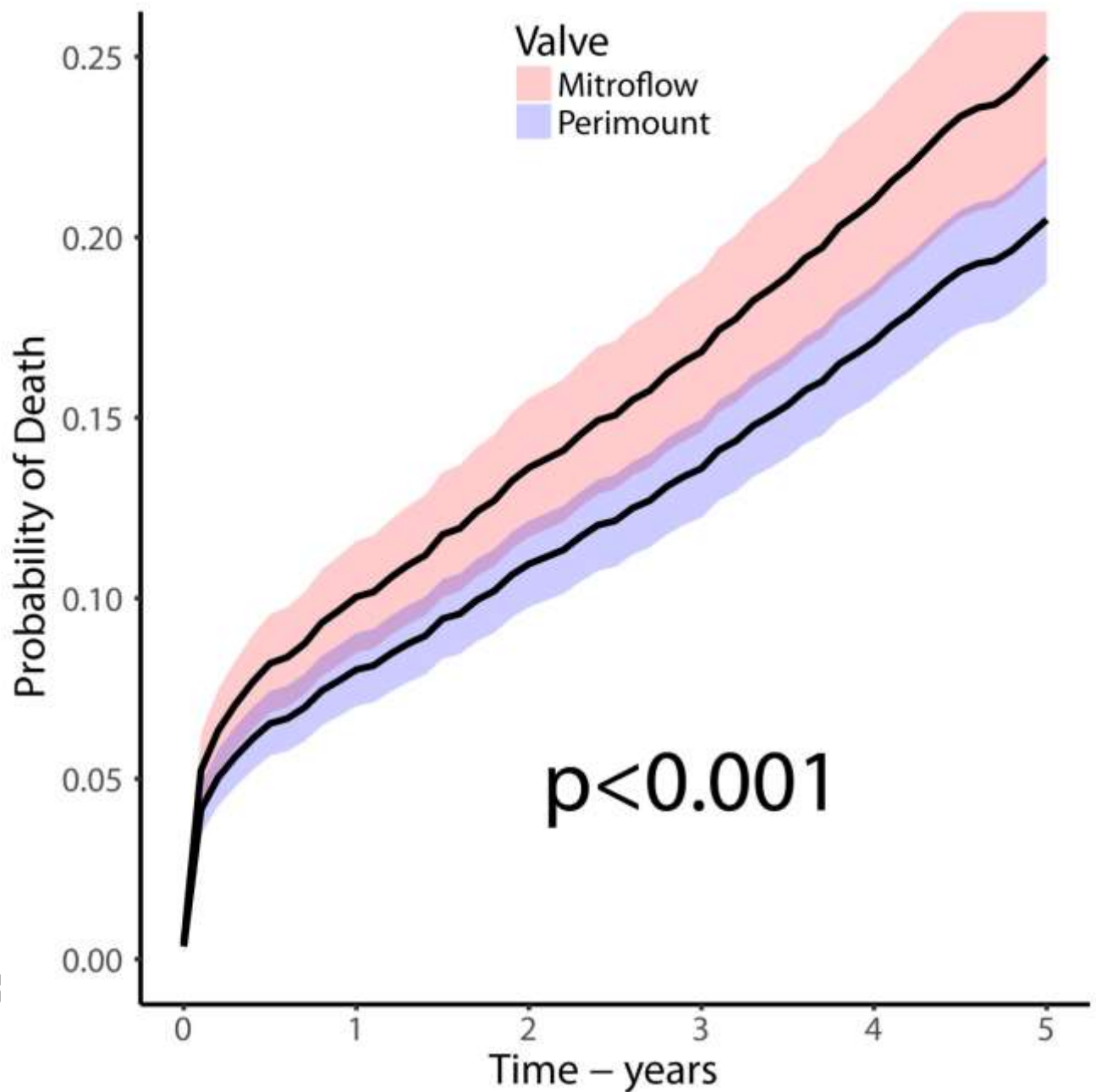
Abbreviations

No abbreviations are used in the manuscript.

ACCEPTED MANUSCRIPT

2 Central picture

- 2 Standardized cumulative mortality curves based on Cox regression comparing the absolute risks of death after surgery in patients with Perimount and Mitroflow aortic valves, respectively, standardized to the characteristics of all patients.



3

2.1 Central message

Both Mitroflow and Perimount aortic valves demonstrate long term durability, but in comparison Perimount valves demonstrated significantly better overall survival.

3.1 Perspective Statement

Both Mitroflow and Perimount aortic valve prosthesis demonstrated long term durability, however, Mitroflow valves were associated with an increased absolute risk of death. Within the limitations of an observational study these results should influence valve choice and also stimulate increased attention during follow up of patients with Mitroflow valves.

3 Abstract

3.1 Objectives

Bioprosthetic aortic valves degenerate over time, and differences between brands could be expected. We compared two brands implanted in three different centers serving 3.3 million people.

3.2 Methods

Between 2000–2014 we identified 1,241 bioprosthetic aortic valve replacements using Mitroflow (Sorin, Milan, Italy) and 3,212 using Perimount (Edwards Lifesciences, Irvine, CA, USA) covering 88% of all aortic valve replacements in the region. Average differences in t-year mortality were derived from Cox regression.

3.3 Results

The complete case analyses included 881 Mitroflow replacements and 2,488 Perimount replacements. The median follow-up time and 25/75 percentiles was 5.0 years (3.3–7.2) and 8.4 (5.1–10.6) years for Perimount and Mitroflow respectively. Multiple Cox regression analyses demonstrated significantly higher mortality with Mitroflow valves compared with Perimount (hazard ratio 1.27; 95% CI: 1.1–1.5; $p < 0.001$). Average risk of death within five years was 25.0% with Mitroflow and 20.4% with Perimount. Average difference in 5-year mortality based on Cox regression was 4.60% in favor of Perimount (95% CI: 1.02–8.02%; $p = 0.01$) and the number needed to harm was 21.9 (95% CI: 12.7–80.5) within five years. Propensity matching confirmed two year survival differences 4.6% in favor of Perimount (95% CI: 1.2–7.9%; $p = 0.004$), and further confirmed in a series of subgroups and a double robust analysis that takes into account both propensity for treatment and covariate relation to outcome.

3.4 Conclusions

Mitroflow valves were associated with a significantly increased risk of death when compared to Perimount valves.

3.5 Introduction

Several studies have confirmed bioprosthetic aortic valve prostheses to be a viable alternative to mechanical valve prostheses, especially in the elderly.¹⁻⁴ Several manufacturers have developed bioprosthetic valves with good long term performance when individually assessed.⁵⁻⁷

Head-to-head comparison of the durability of bioprosthetic replacement valves have been difficult due to inconsistent reporting of results from surgery⁴ despite general consensus for evaluating and reporting the outcomes.^{8,9} However, criticism of Mitroflow replacement valves have risen due to early onset structural valve degeneration,¹⁰⁻¹² and a recent study from one of the centers in the current study comparing Mitroflow valves to alternative Perimount valves supports this initial suspicion.¹³

While the Mitroflow valve has a flat sewing ring, the sewing ring of the Perimount valve is scalloped, following the shape of the aortic annulus. The Perimount valves are made from three pieces of leaflet-material which are suspended in an external “scaffold”, and stitched to this, while the Mitroflow valve is made from one single piece of leaflet material, sutured at one of the three commissures, while the “scaffold” is internal (see supplementary Figure 1).

The available results indicate that durability differences between biological valves may be an issue. Further knowledge of comparative valve durability is thus necessary for appropriate advise to patients. To further investigate these findings and eliminate the possibility of inferior surgical results in a single center, an investigation of complete data from bioprosthetic aortic valve implantations from the entire western region of Denmark, covering

more than 3,3 million individuals, and more than 4,400 aortic valve replacements from three large centers for cardiac surgery were used.

3.6 Methods

In Denmark, all citizens are at birth assigned a unique and permanent civil registration number recorded in the Civil Registration System,¹⁴ and all health services (private and public), including pharmacy dispensations of prescribed drugs, are required by law to be recorded in several nationwide registries. Starting with a clinical database of all cardiac procedures in a population of 3.3 million individuals (The Western Denmark Heart Registry), we identified aortic valve replacements and joined the individuals using the civil registration number to several other government registries with information on causes of death, prescription medication and hospital admissions, to create a complete cohort of individuals with bioprosthetic aortic valves and medical history. Patient prosthetic mismatch was calculated from the patient body surface area and the chosen valves effective orifice area in vitro, and a ratio below 0.85 was considered a mismatch and included as a result.

3.6.1 Study population

The Western Denmark Heart Registry¹⁵ has since 2000 consistently been used to record data from all cardiac procedures performed at the three centers (Odense, Aarhus, Aalborg) that are part of this study. Guidelines for reporting valve replacements surgery can be found at this url: <https://www.sts.org/sites/default/files/documents/pdf/guidelines/Akins.pdf> We identified individuals who had undergone aortic valve replacement with either Mitroflow (Sorin, Milan, Italy) or Perimount (Edwards Lifesciences, Irvine, CA, USA) in the period between 2000 and 2014. The Mitroflow valves used in the present study have prior to publication of the present study been withdrawn and substituted by a model with a different antimineralization

treatment. The National Register for Medicinal Products Statistics¹⁷ was used to identify medication before aortic valve replacement surgery. Medication information was extracted 30 days before aortic valve replacement for all drugs except glucose lowering drugs for diabetes and drugs for hypertension were prescriptions 180 before surgery was included. The Anatomical Therapeutic Chemical Classification System codes (ATC) used are listed in Table 1.

3.6.2 Statistical analysis

3.6.2.1 Descriptive statistics

Data for continuous data were presented as mean with standard deviation, categorical data as counts with percentages. The median potential follow-up time was estimated with the reverse Kaplan-Meier method in both treatment groups separately and reported with inter quartile ranges (IQR; 25% and 75% percentiles).

3.6.2.2 Main analysis

The primary outcome for all analyses was all cause absolute risk of death as a continuous time to event endpoint stopped five years after surgery or at date of administrative censoring (December 31, 2015). The 5-year limit was chosen to justify positive probability of being uncensored across treatments, centers and confounder distribution. The two-year survival status was evaluated as a binary endpoint and reported as difference in survival probability and number needed to harm one patient (one divided by difference in survival probability multiplied by 100). The reason for including two years was that there was no censoring prior to two years. A secondary endpoint was 30-day survival status.

A multiple Cox regression model was used as out main model for the all-cause absolute risk of death, adjusting for all available covariates which include age at surgery groups (<60, 60-

70, 70-80, >80), sex, hypertension, hyperlipidemia, smoking status (current, previous or never), diabetes, myocardial infarction, ejection fraction, creatinine (low, normal or high), bypass surgery, angina, body mass index, priority (acute or elective), endocarditis, ACE inhibitor, beta blocker, diuretic, calendar time (2000-2005, 2006-2008, 2009-2013) and valve size (≤ 21 , 23, 25 or ≥ 27 mm). Information on the surgical center was not included because the positivity assumption was violated for center (zeros occurred in the treatment assignment probability, see supplementary Figure 2). Results were presented as hazard ratios with 95% confidence intervals and p-value for statistical significance. Based on the multiple Cox regression model we also obtained average treatment effects as differences between standardized absolute risk of death within 30 days, two years and five years after surgery and supplied with bootstrap confidence limits based on 200 bootstrap samples (G-formula,²¹⁷). Within the limitations of the observational nature of the data and the validity of the Cox regression model, the so-obtained average treatment effects are comparable to results of a hypothetical study which assigned the treatment group at random to all patients.

3.6.2.3 Sensitivity analyses

In addition, a series of sensitivity analyses was performed.

The Cox model was performed in subsets of the data: all patients younger than 60 were excluded, an analysis where all valves of size ≤ 21 mm were excluded, a separate analysis in center Odense, and in the calendar period 2008–2013.

A sensitivity analysis including only one center (Odense) was included, as well as an analysis replacing time period with surgical center included as a random variable.

To account for potential misspecification of the multiple Cox regression model, a propensity score matching analysis was performed.¹⁸ All propensity score analyses were performed using the complete cases only. Propensity scores were estimated with multiple logistic

regression adjusted for the same variables as included in the multiple Cox regression analysis, see supplementary Figure 3. For each patient we matched one patient of the respective other treatment arm. The match was determined as the patient who had the closest propensity score value in either direction. The two-year survival status was used as outcome for the propensity score matching analysis and reported were differences in the two-year survival probabilities between Mitroflow and Perimount with 95% confidence limits hereby accounting for the uncertainty of the estimation of the propensity score model.¹¹⁸ The results are directly comparable with the two-year results of the main analysis, see Table 3.¹¹⁹

A sensitivity analysis based on multiple imputation was performed using the Substantive Model Compatible Fully Conditional Specification algorithm.²² Multiple imputation results were reported as hazard ratios based on our main Cox regression analysis and 200 imputed datasets where Rubin's rule was used to estimate the standard errors.

Another sensitivity analysis was performed to check bias due to misspecification of the outcome model. We performed a double robust analysis which combines a model for outcome with inverse probability of treatment weighting. The probability of treatment was obtained with the propensity score model. The outcome model was another logistic regression model (same confounder adjustment as main model) for the two-year mortality risk and the main Cox regression model for the 5-year mortality risk. For the 5-year mortality risk we also needed a third model for the probability of censoring weights. The latter was obtained with a Cox regression model for the censoring times. The doubly robust analysis is unbiased if either the treatment propensity score model or the outcome model is correctly specified.²⁰

Data were managed using SAS 9.4 (Cary, NY, USA) for Windows, and statistical analysis with R statistics package (version 3.5) for Windows (R Core Team (2015))²³.

3.6.3 Baseline characteristics

Patient characteristics and characteristics of the matched population are presented in Table 1 and a CONSORT diagram is presented in Figure 1. A total of 5,248 patients received a bioprosthetic aorta valve in one of the three participating centers during the years 2000–2013. Of these 167 were excluded from this study because of simultaneous mitral valve replacement. In 13 cases valve size was missing from the registry, and 615 patients that received other valve types than those compared were excluded. Thus 4,453 patients were included in the study cohort of which 1,241 received a Mitroflow valve, and 3,212 a Perimount valve. The number of reoperations was 22 for Perimount and 36 for Mitroflow, of which 11 versus 5 was due to infection (endocarditis), and 3 versus 31 due to structural valve degeneration, respectively.

An overview of the number of valve replacements by thoracic center is presented in supplementary Figure 2. Only Mitroflow models 12A and LXA have been used. For Carpentier-Edwards Perimount valves type Magna 3000 and Magna Ease 3300 were used. None of the prosthesis used are coated with anti-calcification drugs. PPM information for Mitroflow and Perimount valves were available in 85% and 81% of the cases respectively, and the number of PPM for Mitroflow was 3 (<1%) out of 1,048 versus 337 (15%) out of 2,255 for Perimount.

3.2 Ethical considerations

In Denmark, registry based studies do not require ethical committee approval. The Danish Data Protection Agency has approved the study (GEH-2014-015, I-Suite nr: 02733).

3.7 Results

The median follow-up time was 5.00 and 8.44 years for Perimount and Mitroflow respectively, and for this reason, all survival analyses were stopped at five years. During the

period 1.297 of individuals with Perimount valves died, and 890 with Mitroflow valves.

Number of operations and deaths (%) by label (valve) size are included in Table 1 and Table

2. Causes of death are presented in Table 2. The primary analysis, a Cox model revealed a significant difference in the absolute risk of death in favor of Perimount valves, see Figure 2, Figure 3 and Table 3 for overall analyses and analyses at 30 days, two years and five years.

As surgical center was not in the main model because of violation of the positivity assumption, a subgroup analysis of Odense (Figure 4) was included as well as an analysis replacing time period with surgical center included as a random variable which both resulted in nearly identical result in favor of Perimount ($p=0.002$).

3.7.1 Sensitivity analyses

All sensitivity analysis unanimously demonstrated superiority in survival for Perimount valves.

Figure 4 shows selected subgroups: After 2005 two out of three centers had a clear preference against Mitroflow valves, and only one center (Odense) continued without a clear preference. The figure shows the single center analysis of Odense after 2005. Also shown is an analysis where the smallest valve (21 mm) was excluded, only patients above 60 years of age and only the late part of the study period (2008–2013).

In the propensity matched population the average two-year survival probability for Mitroflow patients compared to Perimount patients was 4.6% lower (95% CI: 1.2–7.9%; $p=0.004$) and the number needed to harm was 21.9 (95% CI: 12.7–80.5) within two years after operation.

Analysis of imputed data using chained equations complete case missing and Cox model with death as endpoint were 1.19 for Mitroflow valves (95% CI: 1.03–1.38; $p=0.02$).

Finally, a double robust analysis which uses inverse probability weighting of propensity scores and also adjusts for covariates influencing outcome was performed after five years.

This analysis revealed an average risk of death difference in favor of Perimount valve of 7.13% (95% CI: 2.97-11.29).

Discussion

In this multi-center study of 4,453 bioprosthetic aortic valve replacements during 2000–2013 with either Mitroflow or Perimount brand valves, we demonstrated good overall long term durability for both, but the direct comparison clearly identified a worse overall survival for Mitroflow valves (Figure 2). The findings were consistently demonstrated on three populations of either propensity matched individuals, the unaltered complete case population and complete cases with imputed missing data. The quality of the statistical methods applied was confirmed by several sensitivity analyses.

These findings are in line S n ge et al,¹² who also found durability problems for Mitroflow bioprosthetic valves compared to alternatives. Despite the comments by Pfeiffer and colleagues²⁴ and the singular valve study by Piccardo et al²⁵, we challenge the statement that this increase can be attributed to Mitroflow valves being selected for a specific subgroup of difficult cases (i.e. small aortic diameter with a resulting increased risk of patient-prosthesis mismatch), as exclusion of small valve diameters did not change the overall findings in this. Not surprisingly, our findings are in conformity with the single-center study by Nielsen et al,¹³ indicating that the increased risk observed in patients with Mitroflow valves are independent of the cardiac surgery center and concomitant medication, as data in that study was part of the current study.

Several follow-up studies based on a singular bioprosthetic valves,^{2,5,6} including Mitroflow,^{26–29} from different institutions are available, but we believe that these findings cannot be used in a head-to-head comparison of aortic valves, which is in contrast with our

cohort which for the most part had selected valve manufacturer based on litigation rather than surgeons choice. Although admittedly local policies between the three centers participating, including treatment practice, patient selection and surgeon preferences may have influenced the choice of bioprosthetic valve used. We believe that the most part of these possible confounding factors are eliminated due to the geographical separation and independent management of each center. Our study therefore strongly suggest, that there are significant differences between valves, but cannot determine the cause.

It is well known that bioprosthetic valves have limited durability due to degeneration is calcification of the biological material, leading to stiffness of the leaflets resulting in stenosis or break down creating incompetence.³⁰ this calcification process is still not fully understood.³¹ Factors such as patient age, tissue fixation, mechanical stress have been shown to influence tissue mineralization, and treatment of the biological tissue with antimineralization agents have been shown to prolong durability.³² We are unable to challenge the possible benefits of antimineralization in our study, as none of the valves used during 2005–2015 included such coating. But to our knowledge no study has yet proven any increase in durability of valves with antimineralization agents, and consequently other studies are needed to assess this.

Due to the seriousness of our findings we have speculated on the possible reasons of the observed increased risk of death for Mitroflow valves. Possibly Mitroflow valves deteriorate faster due to faster calcification, but we cannot know for sure without continuous echocardiographic data, which was not available in the observed cohort. Another theory is how the valves are constructed; Mitroflow valves are made up of a long strip bovine pericardium wedged around three sticks forming the valve commissures, and thus the strain of the mechanical movement of the valve opening and closing is tearing on the pericardium only. In Edwards valves the bovine pericardium flaps forming the valve is sewn onto the

three sticks forming the commissures, and thus the mechanical stress is absorbed by the sewing, which could be more durable than pericardium alone. Finally, the ratio of inner versus outer diameter of the valve differs among the two, which may also play a role.

In summary, the compared valves differ in both materials, construction and geometry/hydrodynamic performance, which may all be factors contributing to faster structural valve deterioration, and increased workload on the left ventricle, eventually leading to increased risk of death. However, we are not able to give a causal explanation to the increased risk of death rate seen in the patients receiving Mitroflow valves, partly because this is a purely observational study, but also because we lack continuous echocardiographic data as well as autopsies of the people who have died, which could reveal important information on possible valve degeneration.

Limitations

The quality of epidemiological data available from the Danish Nationwide Registries may be debated to some minor extent, but the amount of scientific evidence gathered from these databases are very large indeed, and the majority of registries have been quality checked on several occasions. We therefore consider the overall quality of the Danish Registries to be very reliable, and not biased based towards one valve manufacturer.

The non-randomized nature of the data limits the conclusions to be valid only within the following assumptions of the statistical analyses.

The validity of the propensity score matching method relies on the untestable assumption of no unmeasured confounders.¹⁹ The multiple imputation analysis relies on the assumption of missing at random.

Speculations on the reason for the observed increased risk of death in Mitroflow valves is limited by lack of echocardiographic data and possibly inaccurate and incomplete registration of the causes of death in both groups, as only a minor fractions of patients are autopsied.

3.7.2 Implication

This study clearly demonstrates inferiority of Mitroflow bioprosthetic aortic valves compared to Perimount. This should influence the surgeons selection between the two, in favor of the latter regardless of patient. Consequently, we advice that all patients with a Mitroflow valve are closely followed to provide early detection of adverse events in relation to the prosthesis.

The wider implication of the study is that further head-to-head comparisons of bioprosthetic valve durability are necessary. Ideally the findings should be confirmed in a randomized trial including valves with antimineralization treatment, but we generally believe the present findings strongly advise against implantation of Mitroflow valves, which may exclude that possibility due to ethical reasons.

3.7.3 Conclusions

Our findings consistently demonstrate that Mitroflow bioprosthetic aortic valves are associated with a significantly increased risk of death when compared to Perimount valves, from 30 days and at least up until five years following operation.

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The study received no external funding.

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5 Figures

Figure 1; CONSORT diagram.

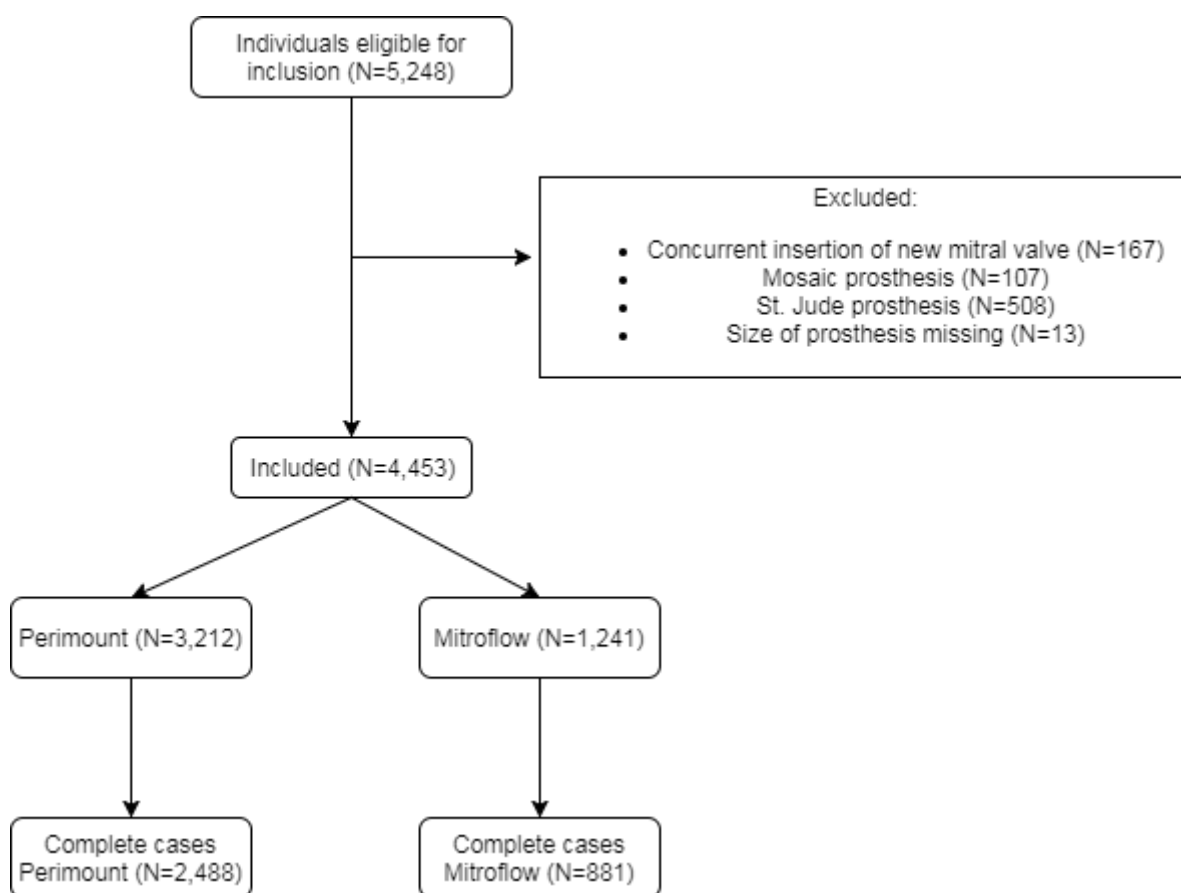


Figure 2; Standardized cumulative mortality based on Cox regression analysis (absolute risk of death) curves comparing Carpentier-Edwards Perimount aortic valves to competitor Sorin Mitroflow including 95% confidence limits. The model was significant in favor of Perimount valves ($p < 0.001$). The shaded areas are 95% confidence limits.

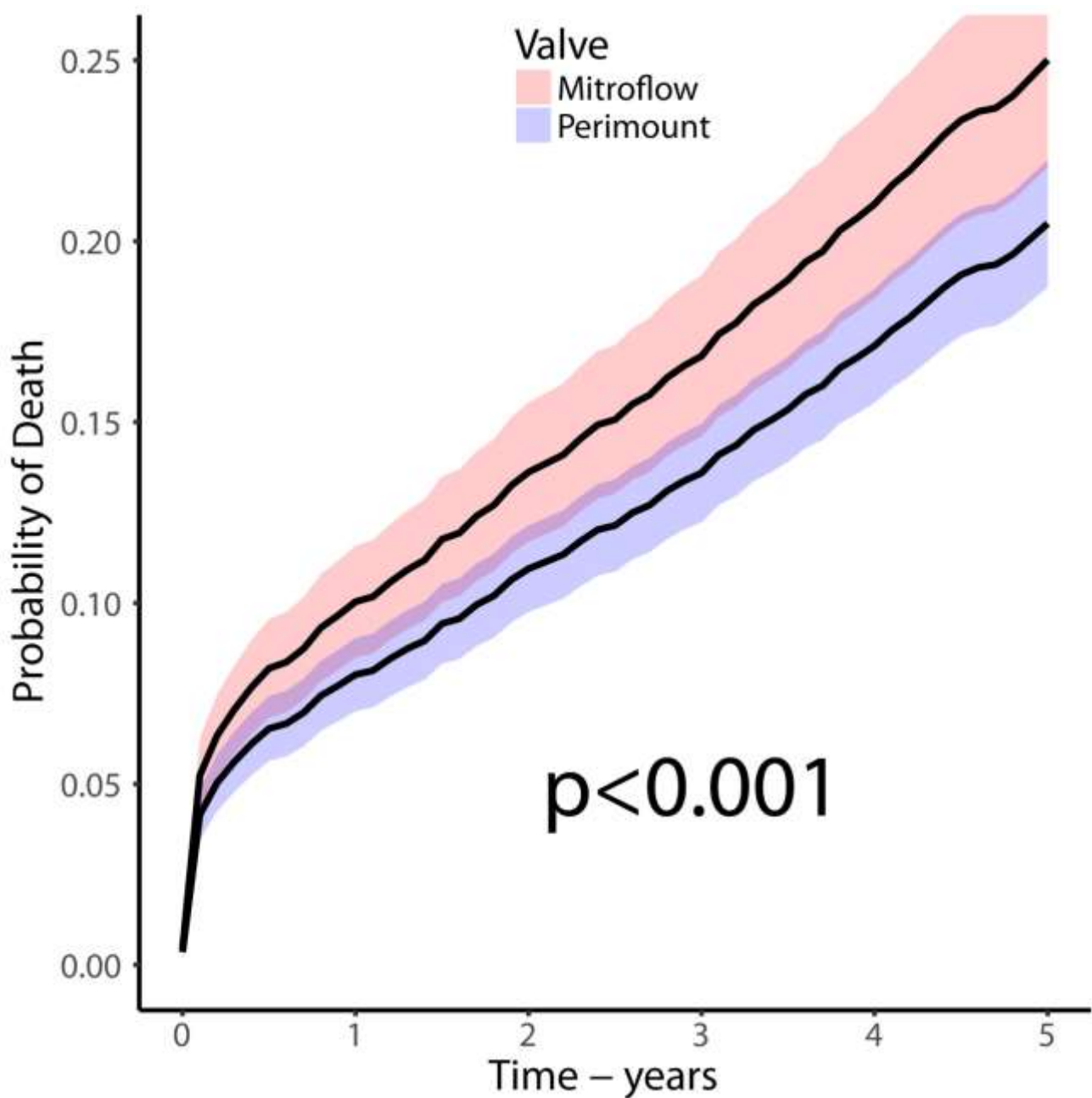


Figure 3; Complete case analysis of all-cause risk of death. Shown are hazard ratios from multiple Cox regression analyses.

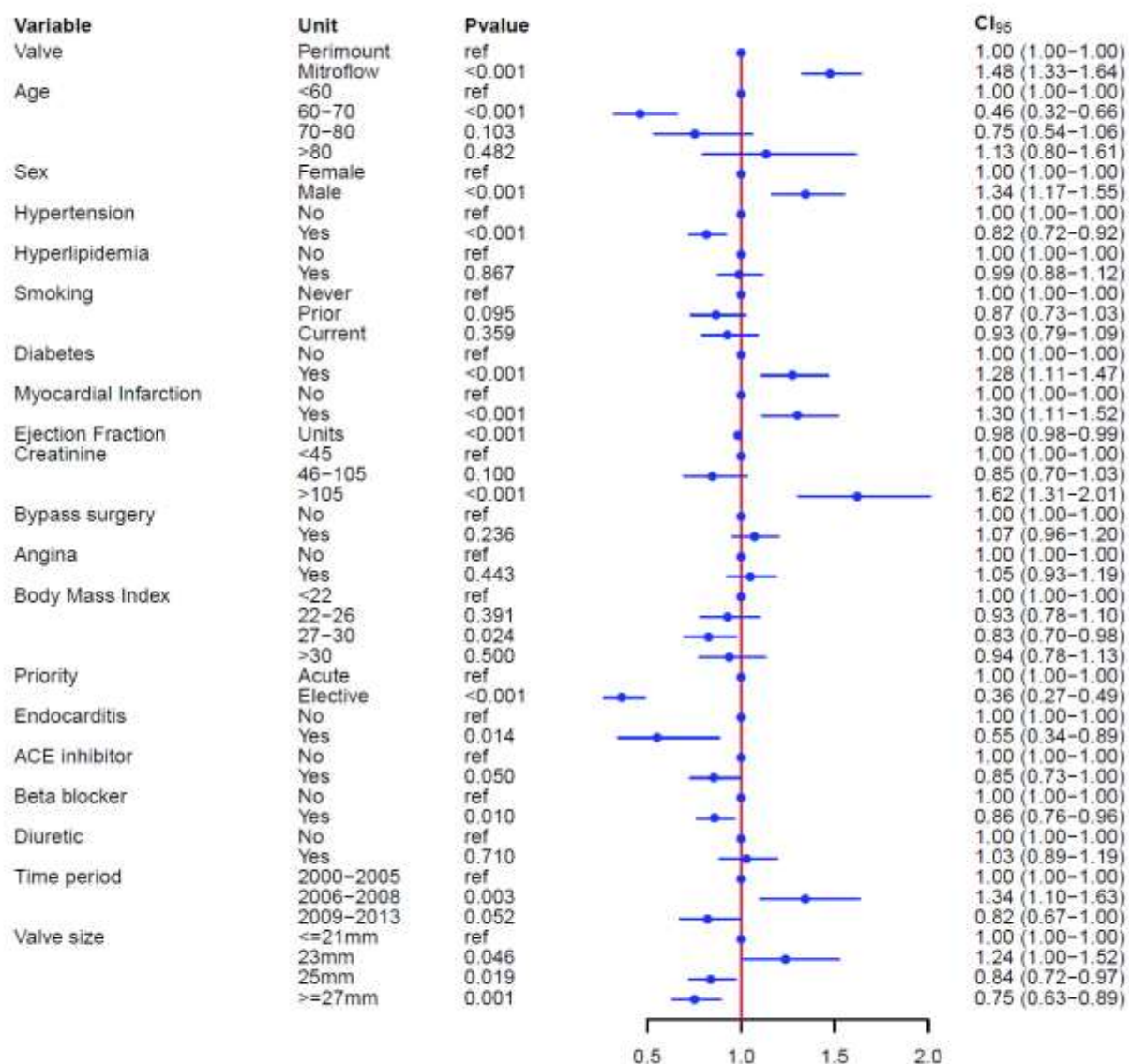


Figure 4; Standardized cumulative mortality based on Cox regression analysis (absolute risk of death) including 95% confidence limits comparing all-cause mortality of Sorin Mitroflow versus Carpentier-Edwards Perimount aortic valves in four subgroups of the population; age above 60, size above 21 mm, Odense surgical center and the period 2008–2013. These curves uses the Cox model to simulate an experiment where each individual in each subgroup receives both treatments. The shaded areas are 95% confidence limits.

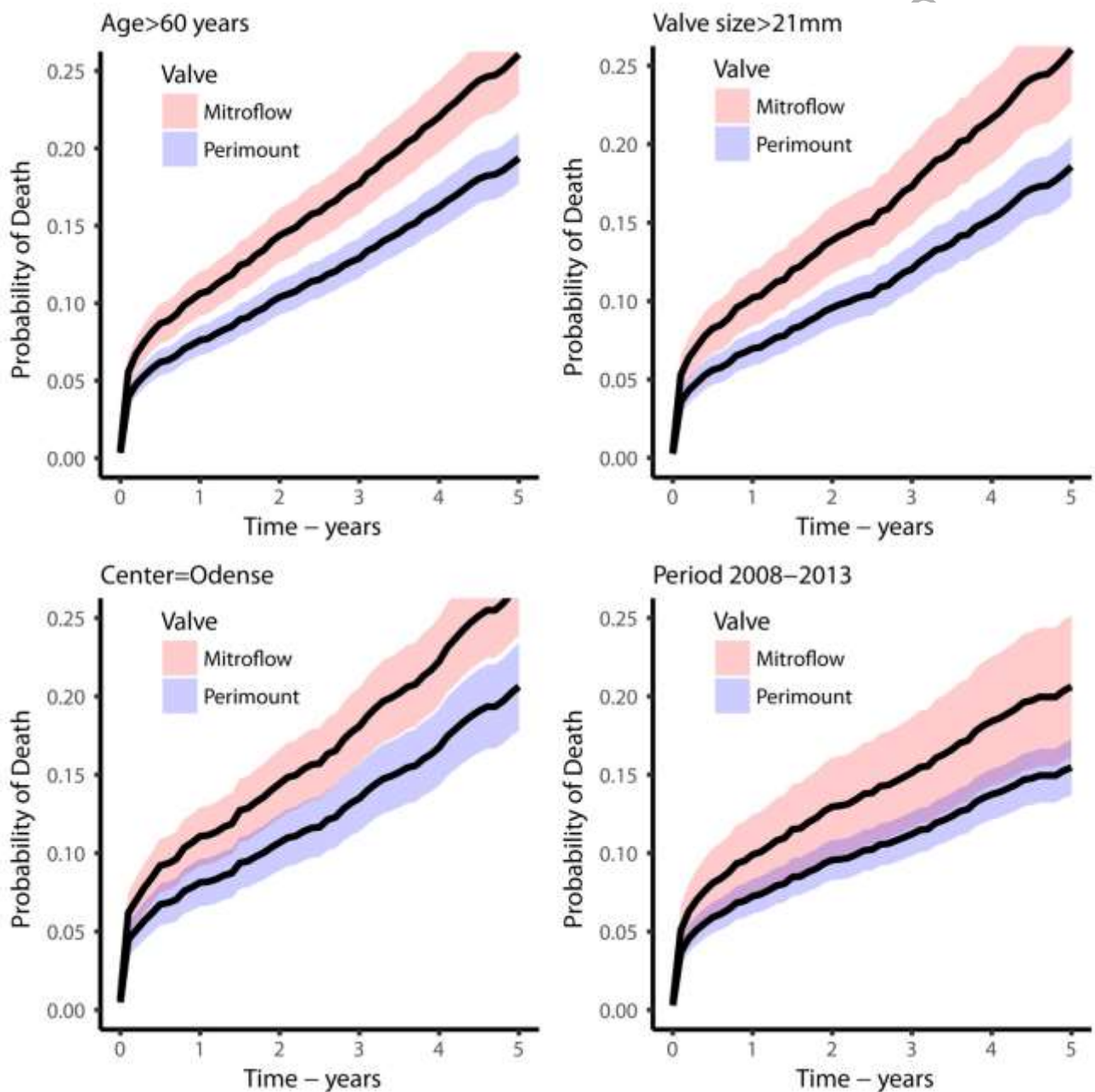
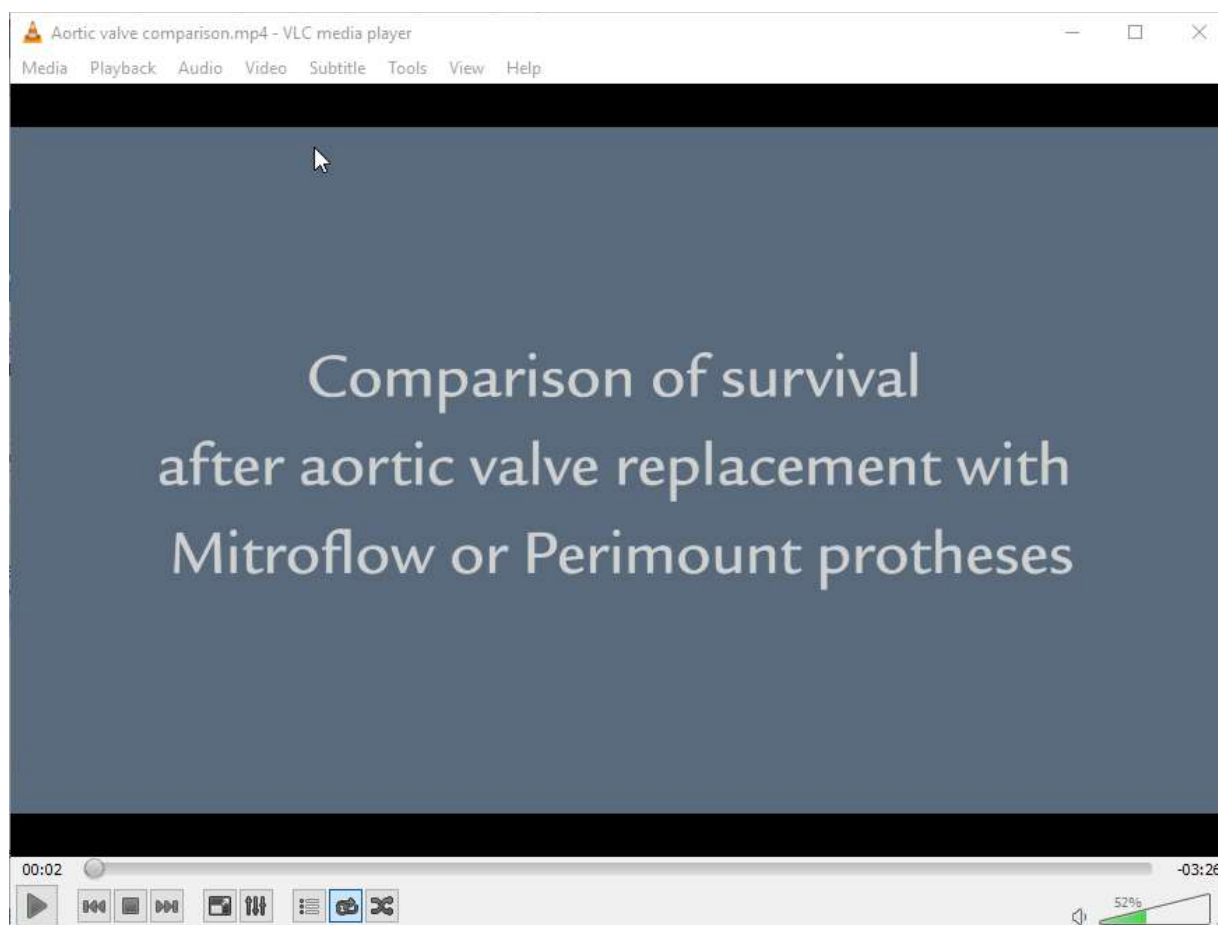


Figure 5; Video describing the study and results.



6 Tables

Table 1. Patient characteristics of observed population and propensity matched population.

Matching paired 881 Mitroflow replaments to 2,488 Perimount replacements both ways to obtain an analysis sample twice the original size. Center was not part of matching (see methods).

Variable	Levels	Perimount	Mitroflow
Total count		3335	1293
Included		3212	1241
Complete cases		2488	881
Follow up (days)	mean (sd)	1358.6 (1098.5)	1880.0 (1257.8)
Age (years)	<60	104 (4.2)	4 (0.5)
	60-70	689 (27.7)	149 (16.9)
	70-80	1283 (51.6)	544 (61.7)
	>80	412 (16.6)	184 (20.9)
	missing	1	0
Sex	Female	875 (35.2)	420 (47.7)
	Male	1613 (64.8)	461 (52.3)
Hypertension	No	935 (37.6)	421 (47.8)
	Yes	1553 (62.4)	460 (52.2)
Hyperlipidemia	No	1052 (42.3)	482 (54.7)
	Yes	1436 (57.7)	399 (45.3)
Smoking	Never	339 (13.6)	103 (11.7)
	Prior	959 (38.5)	393 (44.6)
	Current	1190 (47.8)	385 (43.7)
Diabetes	No	2039 (82.0)	742 (84.2)
	Yes	449 (18.0)	139 (15.8)
Myocardial infarction	No	2214 (89.0)	775 (88.0)
	Yes	274 (11.0)	106 (12.0)
Ejection fraction (Units)	mean (sd)	53.8 (11.3)	54.8 (10.9)
	missing	370	172
Creatinine	<45	175 (7.0)	70 (7.9)
	45-105	1969 (79.1)	654 (74.2)
	>105	344 (13.8)	157 (17.8)
	missing	484	291
Bypass surgery	No	1548 (62.2)	513 (58.2)
	Yes	940 (37.8)	368 (41.8)

Center	Aalborg	314 (9.4)	37 (2.9)
	OUH	1120 (33.6)	813 (62.9)
	Skejby	1901 (57.0)	443 (34.3)
Angina	No	1713 (68.9)	625 (70.9)
	Stable	775 (31.1)	256 (29.1)
Body Mass Index	<22	290 (11.7)	118 (13.4)
	22-26	608 (24.4)	243 (27.6)
	26-30	1052 (42.3)	354 (40.2)
	>30	538 (21.6)	166 (18.8)
Priority	Acute	61 (2.5)	17 (1.9)
	Elective	2427 (97.5)	864 (98.1)
Endocarditis	No	2432 (97.7)	869 (98.6)
	Yes	56 (2.3)	12 (1.4)
ACE inhibitor (before)	No	2121 (85.2)	787 (89.3)
	Yes	367 (14.8)	94 (10.7)
Beta blocker (before)	No	1800 (72.3)	621 (70.5)
	Yes	688 (27.7)	260 (29.5)
Diuretic (before)	No	2167 (87.1)	734 (83.3)
	Yes	321 (12.9)	147 (16.7)
Time period	2000-2005	49 (2.0)	206 (23.4)
	2006-2008	509 (20.5)	341 (38.7)
	2009-2013	1930 (77.6)	334 (37.9)
Valve size	≤21mm	667 (26.8)	327 (37.1)
	23mm	282 (11.3)	67 (7.6)
	25mm	870 (35.0)	237 (26.9)
	≥27mm	669 (26.9)	250 (28.4)

Table 2; *Causes of death by aortic valve. The table shows the number of patients who died at the end of follow-up according to the cause of death. The table does not account for differences in length of follow-up and should not be interpreted directly.*

Level	Perimount (N=3212)	Mitroflow (N=1241)	Total (N=4453)
Blood Pressure	41	31	72
Cancer	167	89	256
Cerebral vascular disease	59	38	97
Endocarditis	44	28	72
Heart failure	62	56	118
Infection	144	96	240
Ischaemic heart disease	189	129	318
No information available	1968	387	2355
Other known causes of	235	143	378

death			
Other cardiovascular	303	244	547

Table 3; Average treatment effect and difference from Cox model

Time point	Average risk of death % (95% CI) Mitroflow / Perimound	Difference % (95% CI)
30 days	5.0 (4.0-6.0) / 4.0 (3.2-4.6)	1.0 (0.21-1.86) p=0.014
2 years	13.6 (9.8-11.7) / 11.0 (9.8-12.1)	2.7 (0.59-4.75) p=0.012
5 years	25.0 (15.1-22) / 20.5 (18.7-22.2)	5.0 (1.02-8.02) p=0.011